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March 8, 2005

VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments Regarding Docket No. 2004P-0068

Dear Sir or Madam:

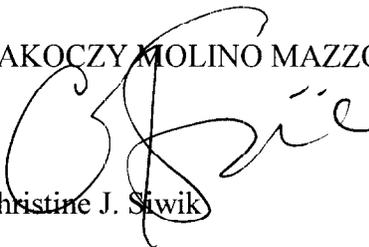
On behalf of our client, Barr Laboratories, Inc., we submit the attached comments in response to the February 2, 2004, citizen petition filed on behalf of Ferring Pharmaceuticals, Inc., regarding the drug desmopressin. Our comments include a statement prepared by Marvin C. Meyer, Ph.D., Emeritus Professor and former Chairman of the Department of Pharmaceutical Sciences and Associate Dean for Research and Graduate Programs at the College of Pharmacy at the University of Tennessee Health Science Center in Memphis, Tennessee.

As required by 21 C.F.R. § 10.30, we include an original and 4 copies of these comments.

Should you have any questions regarding these comments, please do not hesitate to contact me. We appreciate the opportunity to respond to this petition.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP


Christine J. Siwik

CJS/cd
Enclosures

2004P-0068

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**Comments of Barr Laboratories, Inc.
Regarding Docket No. 2004P-0068**

INTRODUCTION

The goal of Ferring's petition is clear – the preservation of its monopoly on desmopressin acetate tablets. While Ferring has used its patent to delay generic market entry, the company apparently does not intend to fight a single-front battle. Instead, Ferring seeks to elicit the Agency's assistance with its generic-blocking strategy, asking FDA to erect what Ferring hopes will be virtually insurmountable regulatory barriers to generic market entry. Ferring's petition is, however, based upon erroneous assumptions and poor science. Desmopressin acetate does not present any unique issues with respect to establishing bioequivalence. A generic company can establish bioequivalence to Ferring's DDAVP[®] tablets without jumping through the scientifically unnecessary, expensive, and (not surprisingly) time-consuming hoops Ferring advocates. The Agency should see Ferring's petition for what it is, and deny that petition in its entirety.

DISCUSSION

According to Ferring, "the unusual if not unique properties of orally administered desmopressin call into question the reliability of conventional bioequivalence study procedures and data, mandating that all ANDA sponsors should present additional evidence from appropriately designed studies in children to establish bioequivalence to the RLD." (Ferring Pet. at 3). Ferring is mistaken. Conventional bioequivalence study procedures and data can reliably assess and establish the bioequivalence of a generic desmopressin acetate tablet product to the reference listed drug ("RLD"). ANDA applicants do not have to conduct clinical end-point studies in children (let alone enuretic children) to demonstrate bioequivalence. Bioequivalence can be readily established using properly designed pharmacokinetic ("PK") studies.

Even if Ferring genuinely believes its own arguments, they nevertheless originate from Ferring's own poorly conducted studies. That Ferring, back in the early 1990s, had difficulty designing proper PK studies does not mean that such studies cannot be carried out. Indeed, as explained in the attached expert statement, PK studies can be used to assess bioequivalence of generic desmopressin acetate products. (*See* Statement of Marvin C. Meyer, Ph.D., attached hereto as Exhibit A). Ferring's petition should be denied.

I. A Proper PK Study Is Sufficient To Establish Bioequivalence Of Generic Desmopressin Acetate Products And Additional Testing Should Not Be Required.

A. PK Studies Are Appropriate To Establish Bioequivalence Of A Generic Desmopressin Acetate Tablet Product.

Ferring concocts a host of alleged problems with PK testing of desmopressin. According to Ferring, because desmopressin is given in microgram doses, has low oral absorption, has a low effective plasma concentration and may be difficult to assay, a PK study is insufficient to establish bioequivalence. (Ferring Pet. at 1, 5-6). Ferring is incorrect, both from a regulatory standpoint and as a factual matter. Such problems simply do not exist.

1. A PK Study Is FDA's Most Preferred Study And Is Sufficiently Sensitive To Establish Bioequivalence.

FDA repeatedly has affirmed that PK studies are the gold standard for establishing bioequivalence, particularly for orally administered, systemically acting drug products, such as desmopressin. In its regulations, FDA lists "in descending order of accuracy, sensitivity and reproducibility" the types of evidence that the Agency will accept to establish bioequivalence. 21 C.F.R. § 320.24(b). The first and best option, "particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream," is a PK study. *Id.* § 320.24(b)(1)(i).

FDA has further concluded that only where a PK approach is *not possible* should another approach, like a pharmacodynamic ("PD") or clinical study, be used. (*See Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, at 9-10 (2003) ("BA/BE Guidance")). In fact, FDA has concluded that:

Pharmacodynamic studies are *not recommended* for orally administered drug products when the drug is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish BE. However, in those instances where a pharmacokinetic approach is *not possible*, suitably validated pharmacodynamic methods can be used to demonstrate BE.

(*Id.* at 9 (emphasis added)). In addition, FDA regulations confirm that the clinical end-point studies suggested by Ferring are the "least accurate, sensitive and reproducible" approach of all. 21 C.F.R. § 320.24(b)(4). Ferring offers the Agency no legitimate reason to disregard its own regulations and Guidances.

Ferring has failed to establish that an ANDA applicant cannot carry out an appropriate PK study with respect to desmopressin. According to Ferring, because the effective plasma levels of desmopressin are so low, conventional PK studies are insufficiently sensitive to detect the existence of desmopressin, even if desmopressin is present and having some effect. (Ferring Pet. at 6-7). But Ferring bases this argument solely on its own inability to properly design a PK study using radioimmunoassay. For instance, Ferring argues that Ms. Troendle, an FDA group leader responsible for reviewing desmopressin, commented on the difficulty of demonstrating drug absorption because only a small fraction of the drug dose is expected to be absorbed. (*Id.* at 14-15). Her comments, however, speak only to Ferring's own use of an assay with insufficient sensitivity, which Ferring did not properly validate. (Meyer Stmt. at 4). Ms. Troendle's comment does not support Ferring's argument that PK studies, in general, are not sensitive enough to establish bioequivalence for desmopressin. (*Id.*).

Further, in asking FDA to leap to the unwarranted conclusion that, because some assays might not be sufficiently sensitive, no ANDA applicant can carry out an accurate PK

study, Ferring neglects two significant points. First, Ferring ignores its own implicit acknowledgement that not all bioanalytical methods lack the sensitivity necessary to detect the low effective blood levels of desmopressin. (Ferring Pet. at 6 (arguing only that the levels are “below the LLOQ for *most* bioanalytical methods”) (emphasis added)). Second, Ferring ignores the fact that more modern assays exist today – assays that are sufficiently sensitive to detect the effective plasma levels of desmopressin. (*See id.*, Tab 1 (Robertson Stmt.) at 3). Sensitive assays, such as LC/MS/MS, can detect blood levels of desmopressin below the effective level cited by Ferring. (Meyer Stmt. at 4). This type of assay is sufficiently sensitive to do an accurate PK assessment for purposes of establishing bioequivalence. (*Id.*).

An accurate PK study is, therefore, possible with respect to desmopressin. Under FDA’s regulations and Guidance, the fact that an ANDA applicant may readily conduct an accurate PK study for desmopressin should end the matter. FDA should not impose additional requirements on desmopressin ANDA applicants – requirements which would run contrary to the Agency’s own regulations – simply because Ferring was unable to properly design its own studies and chooses to ignore the highly sensitive assays available to ANDA applicants today.

2. Ferring Offers FDA No Legitimate Reason To Depart From The Agency’s Bioequivalence Regulations.

Requiring ANDA applicants to conduct studies beyond the PK studies described in FDA’s regulations would be particularly inappropriate here because Ferring offers neither regulatory authority nor precedent for FDA to abandon its regulations when it comes to desmopressin. Section 320.33 does not, as Ferring suggests, recommend additional bioequivalence criteria beyond a PK study for a drug product with purportedly unique properties. (Ferring Pet. at 12-13). The regulation merely sets forth considerations for determining whether certain drug products may or may not qualify for an *in vivo* bioequivalence waiver under 21 C.F.R. § 320.22. *See* 21 C.F.R. § 320.22(c) (requiring FDA to waive *in vivo* bioequivalence requirement for certain drugs unless FDA evaluated drug under § 320.33 and rated it as having potential bioequivalence problem); *see also* 64 Fed. Reg. 7897, 7897-98 (Feb. 17, 1999) (observing that § 320.33 sets forth criteria to assess whether an applicant may demonstrate bioequivalence for a drug product through *in vitro* studies alone or whether *in vivo* studies will also be required); Meyer Stmt. at 4 (observing that § 320.33 summarizes reasons for requiring *in vivo* bioavailability and bioequivalence data, instead of permitting applicants to rely only on *in vitro* data, and does not address how to determine bioequivalence).

No one disputes that *in vivo* PK studies are required for desmopressin acetate tablets. The only dispute is whether FDA should accede to Ferring’s demands by requiring additional and, according to FDA regulations, inferior studies to establish bioequivalence. Contrary to Ferring’s suggestion, § 320.33 has no bearing on the issue of how to determine bioequivalence. (Meyer Stmt. at 4).

Additionally, Ferring suggests that some sort of precedent exists that would force FDA to require additional studies for products including desmopressin or its salts. (Ferring Pet. at 13-14). Ferring's argument is misguided. In making this argument, Ferring points to statutory and regulatory bioequivalence requirements for drug products that act locally at the site of administration and not via the systemic circulation. (*See id.* at 14 (citing 21 U.S.C. § 355(j)(8)(C) and Draft Guidance for Industry, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing and Controls Documentation*, at 3 (1998) ("MDI Guidance"))). But FDA's decision to impose special requirements for metered dose inhalers ("MDIs") has no relevance for determining whether a PK study for the oral dosage form of desmopressin is adequate to establish bioequivalence.

A drug product delivered through an MDI raises different issues since the drug product is intended to act locally at the site of administration and is not intended to be absorbed into the bloodstream. (*See MDI Guidance*). FDA promulgated special bioequivalence requirements for MDIs specifically because it was concerned that measurement of blood levels of these types of drugs, if such measurements are even possible, may not accurately characterize the amount of drug that actually reached the biological target. (*See MDI Guidance* at 3; Meyer Stmt. at 4).¹ But desmopressin acetate tablets present no such concern. Desmopressin does not act locally in the gastrointestinal tract, but rather is absorbed into the bloodstream and acts systemically. This is precisely why a PK study measuring blood levels of the drug is the most appropriate way to determine bioequivalence. *See* 21 C.F.R. § 320.24(b)(1)(i). (*See also* Meyer Stmt. at 4). Ferring offers the Agency no reason to find otherwise.

3. Ferring Exaggerates Its Concerns Over Desmopressin's Purportedly Unique Properties.

Ferring's purported concerns about desmopressin's characteristics and their effect on bioavailability are exaggerated. FDA's PK approach to demonstrating bioequivalence applies equally to all chemical classes of drugs. Desmopressin is a chemically modified peptide, subject to gastro-intestinal degradation, and is poorly absorbed. While these qualities arguably might make it more technically challenging to conduct a PK study meeting FDA requirements, they neither preclude the use of an acceptable PK study, nor render the conclusion of bioequivalence from such a study invalid. The PK approach to demonstrating bioequivalence applies to all systemically acting, orally administered drugs, regardless of chemical class or extent of absorption. Ferring presents no evidence from which FDA can reasonably conclude that desmopressin behaves any differently than other systemically acting, orally administered drugs.

Ferring contends, for example, that due to desmopressin's allegedly unique properties, the duration of action between two different formulations may be different. (Ferring Pet. at 6-7). Stated differently, Ferring claims that two desmopressin acetate products that

¹ Calcitonin, another drug product cited by Ferring (Pet. at 13-14), also is irrelevant to the issue raised here because calcitonin is dosed intranasally or by injection.

otherwise meet FDA requirements for bioequivalence will nevertheless exhibit a different onset, maximum effect, or duration of action from one another. But the Agency's entire bioequivalence approach and policy is premised on the fact that two products that are bioequivalent will be therapeutically equivalent. (See FDA/CDER, *Approved Drug Products with Therapeutic Equivalence Evaluations*, Preface (24th ed.) ("A major premise underlying the [Hatch-Waxman Act] is that bioequivalent drug products are therapeutically equivalent and, therefore, interchangeable."); Meyer Stmt. at 2). Ferring fails to come forward with any evidence that would warrant FDA altering the fundamental principles upon which the Agency approves generic drug products and major product formulation changes. Thus, Ferring offers the Agency no reason to require additional testing on a product that has already been established as bioequivalent through a PK study. (See Meyer Stmt. at 2).

Moreover, research published by Aventis, the NDA-holder for DDAVP[®] tablets, suggests that desmopressin is not, in fact, sensitive to differences in formulations. A few years ago, Aventis sponsored a study comparing the PK and PD profiles of whole, chewed and crushed desmopressin tablets, and oral solution. See Argenti, D., *et al.*, *A Pharmacokinetic and Pharmacodynamic Comparison of Desmopressin Administered as Whole, Chewed and Crushed Tablets, and as an Oral Solution*, J. Urology, Vol. 165, 1446-1451 (May 2001) ("the Argenti Article"), attached hereto as Exhibit B. That study concluded that desmopressin absorbed via the administration of crushed or chewed tablets or an oral solution had the same effect on urine volume and osmolality as desmopressin absorbed via the administration of tablets swallowed whole. *Id.* at 1451. The results of Aventis' study are evidence that formulation differences between two desmopressin products will *not* result in different onset, maximum effect, or duration of action. (Meyer Stmt. at 2-3). Perhaps these results explain why Ferring, and not the NDA-holder Aventis, submitted the instant citizen petition.

Ferring further asserts that the purported difference in duration of action between different formulations could cause a risk of hyponatremia. (See Ferring Pet. at 7). Even if different formulations create different effects, Ferring overinflates the risks. (Meyer Stmt. at 2). Dr. Robertson, whom Ferring retained to submit comments on its behalf, contends that if clearance of desmopressin from the body is prolonged beyond eight hours, which he calls "the optimal time for treatment of nocturnal enuresis," the body may not fully compensate for any lingering antidiuretic effects of the desmopressin by the time the next dose is taken the following night. (Ferring Pet., Tab 1 (Robertson Stmt.) at 4-5). This could cause hyponatremia, according to Dr. Robertson. (*Id.*). Ferring's theory is a far-fetched hypothetical scenario. Ferring provides no evidence that the absorption of desmopressin can be delayed long enough for hyponatremia to be possible from a single dose. In order for this to happen, a significant proportion of the desmopressin would have to be delivered many hours later than for the RLD. (Meyer Stmt. at 2). If this were the case, it would be readily detected in the bioequivalence study. (*Id.*). Further, the delivery of a significant portion of desmopressin many hours later than the RLD does not seem to be physiologically possible. A study by d'Agay-Abensour, *et al.*, indicates that absorption of desmopressin from the lower regions of the gastrointestinal (GI) tract (where absorption

necessarily would have to take place in order to have such a prolonged effect as to present a hyponatremia risk for a once daily dose) is much lower than from the upper GI tract. *See d'Agay-Abensour, et al., Absolute bioavailability of an aqueous solution of 1-deamino-8-D-arginine vasopressin from different regions of the gastrointestinal tract in man, Eur. J. Clin. Pharmacol. (1993) 44:473-476, attached as Exhibit C hereto. (See also Meyer Stmt. at 2).* The fraction absorbed from the upper GI tract (stomach, duodenum, and jejunum) was 0.19 - 0.24%, whereas the fraction absorbed from the lower GI tract (ileum, colon, and rectum) was only 0.03 - 0.04%. (d'Agay-Abensour at 475; Meyer Stmt. at 2).

Ferring also argues that a desmopressin dose requires careful titration. (Ferring Pet. at 3, 13). Even if true, this does not preclude the use of PK parameters to determine bioequivalence. For other, far more sensitive drugs, most notably warfarin, FDA has concluded that PK studies showing bioequivalence to the RLD are sufficient to establish the safety and efficacy of the generic product, despite the careful dose titration required. (Meyer Stmt. at 3). Once bioequivalence through a PK study is established, what dose to employ should be the same for either the RLD or the generic desmopressin acetate product. (*Id.*).

Ferring also contends that desmopressin exhibits high inter- and intra-subject variability as compared to other drug products. (Ferring Pet. at 5-6). As an initial matter, this contention, if accurate, undermines Ferring's concern about dose titration and complaint that even a slight variance in duration of action may cause hyponatremia. If careful dose titration is required and small variations in duration of action cause such a significant safety risk, this would suggest desmopressin has a narrow therapeutic index. If, however, desmopressin exhibits a high variability in AUC, this would suggest the body is not terribly sensitive to desmopressin levels, and thus that desmopressin does not have a narrow therapeutic index. (Meyer Stmt. at 3). Ferring cannot have it both ways. But more to the point, while subject variability issues may make it more difficult for an ANDA-filer to satisfy FDA requirements for bioequivalence, it is not a reason to reject a PK study as a means of establishing bioequivalence. (*Id.*). Whether an ANDA product exhibits high intra-subject variability could affect whether the product ultimately falls within the confidence limits of the PK study, but it has no bearing on whether a PK study is an appropriate method for determining bioequivalence. (*Id.*).

Ferring further contends, without support, that variability can be reduced by taking the drug on an empty stomach, implying that food may affect drug release. (*See Ferring Pet., Tab 1 (Robertson Stmt.) at 5-6*). Ferring's contention simply is not credible given the fact that the labeling for DDAVP[®] tablets says nothing about food effect. (Meyer Stmt. at 3).

In sum, none of Ferring's purported concerns about desmopressin call into doubt the validity of using PK studies to establish bioequivalence, as provided under FDA regulations. Desmopressin does not present any issues unique from other drugs intended to be absorbed into the bloodstream. FDA should not abandon its well-established policies regarding the acceptability of and preference for PK studies to establish bioequivalence.

B. PD Testing Would Be Not Only Unnecessary, But Also Ineffective In Establishing Bioequivalence.

Ferring's arguments in favor of requiring PD testing have less credibility than its objections to PK studies. Not only does FDA view PD studies as inferior to PK studies in assessing bioequivalence of drug products intended for absorption in the bloodstream, but Ferring's own petition and studies illustrate the shortcomings of using PD testing to establish bioequivalence of desmopressin.

In FDA's view, "[p]armacodynamic studies are *not recommended* for orally administered drug products when the drug is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish [bioequivalence]." (BA/BE Guidance at 9 (emphasis added)). Thus, FDA recommends using PD studies to establish bioequivalence only when PK studies are not possible. (*Id.*) As discussed above, PK studies for desmopressin not only are possible, but are more than adequate to establish bioequivalence. The PD studies that Ferring proposes are thus unnecessary.

Additionally, PD studies likely would be insufficient to determine bioequivalence in the case of desmopressin. (Meyer Stmt. at 5). Even Ferring acknowledges this. While asking FDA to require ANDA applicants to measure urinary osmolality and urine output, Ferring concedes that these biomarkers have not been prospectively validated against clinical endpoints. (Ferring Pet. at 10). Ferring further acknowledges that "[t]here is no established correlation between an increase in urine osmolality and clinical response to desmopressin in [Primary Nocturnal Enuresis] (PNE) and it has never been shown that a decrease in urine production leads to dryness (clinical effect)." (*Id.* at 11).

Ferring's own studies also suggest that a PD test would be ineffective in establishing bioequivalence. In Study 1, for instance, there was only a 10-15% difference in urine flow rate and urine osmolality, comparing doses of 0.2 and 0.4 mg desmopressin. (Meyer Stmt. at 5; NDA 19-955, Chen, Tien-Mien, Ph.D., Review of Two Pharmacokinetic Studies in a New NDA, at 17, filed 4/20/93 ("Chen Review")). This result suggests that a PD test would not be sufficiently sensitive to assess differences in bioequivalence between two products. (Meyer Stmt. at 5).

Finally, FDA should also reject Ferring's suggestion that single-dose as well as multiple-dose PK and PD studies are necessary to establish bioequivalence. (Ferring Pet. at 15). FDA, for example, does not recommend or require multiple-dose PK studies because they are less sensitive to formulation differences than single-dose studies. (BA/BE Guidance at 8, 12). For immediate release products, FDA recommends a single-dose study. (*Id.* at 12). FDA has no reason to reverse course and require repeated-dosing studies for desmopressin. (Meyer Stmt. at 5). Ferring certainly offers no such reason.

C. Clinical Trials To Show Safety And Efficacy Are Unnecessary.

Ferring also suggests that “comparative clinical trials probably would provide the surest measure of equivalent efficacy and safety.” (Ferring Pet. at 10). FDA, however, views clinical studies as less reliable than even PD studies to establish bioequivalence. *See* 21 C.F.R. § 320.24(b)(4). Indeed, the Agency’s own regulations state that a clinical trial approach “is the *least accurate, sensitive and reproducible* of the general approaches for . . . demonstrating bioequivalence.” *Id.* (emphasis added). FDA has therefore concluded that only “[w]here there are no other means” should a clinical trial approach be used to provide evidence of bioequivalence. (BA/BE Guidance at 9-10). As discussed above, other, and more preferred, means for establishing bioequivalence exist with respect to desmopressin (*e.g.*, PK studies). (Meyer Stmt. at 1-2, 4). FDA should not require ANDA applicants to conduct clinical trials under these circumstances.

Even Ferring itself does not appear to take its own suggestion seriously. Ferring offers no data in support of a clinical studies requirement, nor any reason to adopt such a requirement. Instead, it asserts that clinical studies “probably” would provide the best measure of bioequivalence. (Ferring Pet. at 10). Ferring then undermines this already equivocal assertion by arguing that PK and PD studies should be sufficient to establish bioequivalence. (*Id.* at 10-11). And Ferring cannot rely on its purported concerns about the bioavailability of desmopressin to support its request for clinicals. As discussed above, those concerns are exaggerated and based on FDA requirements for dosage forms of drugs that, unlike desmopressin, are not intended to be absorbed into the bloodstream. Ferring thus offers no valid reason for FDA to require clinical studies to establish bioequivalence for desmopressin.

II. Studies On Enuretic Children Are Unnecessary.

In addition to asking FDA to force ANDA applicants to perform additional and unnecessary studies to establish bioequivalence, Ferring requests that the Agency erect an additional roadblock to generic market entry – the testing of ANDA products on enuretic children. (Ferring Pet. at 8, 15-16). Ferring has no factual basis for making this request. Instead Ferring relies (yet again) on suggestion, speculation, and irrelevant observations. The factual evidence that does exist – research conducted on Ferring’s behalf – supports the use of healthy adults to establish bioequivalence in all patient populations.

A. Ferring Offers No Reason For FDA To Require Studies In Enuretic Children.

Absent data demonstrating that a generic desmopressin acetate product is bioequivalent to the RLD in adults but nevertheless is not bioequivalent in children, there is no legitimate reason to require ANDA applicants to test their products in children. Ferring, of course, offers no such data. Instead, Ferring suggests that bioequivalence between children and adults *may* be different because children “generally have different pharmacokinetics and

metabolism than adults,” the difference “in GI absorption between children and adults may vary depending on the formulation,” and a child’s dose cannot be extrapolated from an adult dose. (Ferring Pet. at 8, 15). Ferring’s arguments lack merit.

First, it would be unethical to conduct PK studies in vulnerable populations such as children unless such studies were absolutely necessary. FDA specifically recommends that “unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies be 18 years of age or older and capable of giving informed consent.” (BA/BE Guidance at 7). *See also* 63 Fed. Reg. 66632, 66640-41 (Dec. 2, 1998) (“FDA . . . does not currently require bioequivalence studies to be conducted in children for generic drugs.”); 65 Fed. Reg. 19777, 19779 (Apr. 12, 2000) (“Bioequivalence comparisons of pediatric formulations with the adult oral formulation typically should be done in adults.”).

While FDA recommends conducting PK studies in children in order to determine the appropriate dose level to use in clinical safety and efficacy studies (*see* Draft Guidance, *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products*, at 4 (Nov. 1998)), nothing would warrant subjecting young children (typically as young as six years old) to the discomfort of extensive blood sampling as part of an additional and unnecessary PK study, the sole value of which is to help Ferring maintain its monopoly on desmopressin acetate tablets. Indeed, these ethical considerations underlie FDA’s recommendation that adults be used for bioequivalence studies. Moreover, the need to minimize blood volumes (especially with young children with PNE), the allegation that only children with enuresis should be dosed, and the alleged poor sensitivity of the assays (which necessitates collection of large blood samples) all make Ferring’s proposal to conduct studies in enuretic children untenable and ill-conceived.

Second, even if Ferring established that the PK of desmopressin is different in children, this would not preclude the use of PK data from adults to establish bioequivalence. When filing an ANDA, generic manufacturers are not trying to extrapolate an appropriate children’s dose. Rather, they are trying to establish bioequivalence between two different formulations using comparative studies. Comparative PK studies in adults are not only perfectly acceptable, but also are the preferred means for establishing bioequivalence between two formulations. Likewise, even if Ferring established that the metabolism, distribution, and excretion of desmopressin are different in children compared to adults, this would not be relevant to a bioequivalence study with a crossover design. (Meyer Stmt. at 5). A number of drugs are indicated for use in children, but FDA does not require bioequivalence studies on those drugs to be conducted in children despite the differences in metabolism and PK. (*Id.*).

Third, Ferring contends that the difference in gastrointestinal absorption of desmopressin between adults and children “may” vary, depending on formulation. (Ferring Pet. at 8). Ferring offers no data to support this contention, nor does it explain how this contention, even if true, would be relevant to establishing bioequivalence. (Meyer Stmt. at 6). Moreover, as discussed above, published research suggests that the absorption of desmopressin is not

particularly sensitive to formulation differences. *See supra* Section I.A.3 (discussing the Argenti Article).

Finally, Ferring argues that one cannot extrapolate a child's dose from the adult dose. (Ferring Pct. at 8, 15). Even if true, this is irrelevant to whether FDA should require studies on enuretic children. (Meyer Stmt. at 3). The issue of what dose to employ in a child is not a bioequivalence issue. (*Id.*). According to FDA, Ferring has established the proper dosing of desmopressin for children. Once bioequivalence to the RLD is established through PK studies, the question of which dose to employ in a child should be the same whether a physician is prescribing the RLD or the generic product. (*Id.*).

B. Studies Conducted On Ferring's Behalf Used Healthy Adult Subjects To Establish Bioequivalence And Bioavailability.

Ferring has failed to establish that studies on enuretic children are necessary to establish bioequivalence. And the research and studies conducted on Ferring's own behalf further undermine its current position that FDA should require such studies. For example, a number of studies in Ferring's NDA were based on or included healthy, normal adults. (Meyer Stmt. at 6; Chen Review at 2). For instance, Aventis relied on studies of healthy male subjects in Study 1 and Study 2 to establish the bioavailability of the RLD. FDA found these studies "acceptable" to establish desmopressin's bioavailability. (Chen Review at 2, 4).

Moreover, in the Aventis-sponsored study that compared the bioavailability of desmopressin from whole, chewed and crushed tablets and oral solution, the authors used healthy, orally hydrated, adult male human subjects. *See* the Argenti Article at 1446. The authors provided their reason for using a homogenous group of healthy males as their subjects. Notably, this reason directly conflicts with Ferring's stated position in the petition. According to the authors, using a homogenous population in bioequivalence testing helps minimize external sources of variability such as age, gender, or disease states on the PK or PD of various treatments. *Id.* at 1449. Reducing the variability, they say, makes it easier to isolate the performance of the test treatment and make statistically relevant comparisons between it and the reference treatment. *Id.* As a result, "[a]fter the tested treatment is deemed bioequivalent, this treatment is *interchangeable* with the reference treatment. The expectation is that the test and reference treatments perform equivalently in an individual *regardless of age, gender or disease state* since drug absorption and disposition have been shown to be independent of the treatment formulation." *Id.* (emphasis added). In other words, the authors of an Aventis-sponsored, peer-reviewed journal article concluded that the age and disease state of the subjects used in the testing is not relevant to the safety and efficacy of the desmopressin formulation, as long as bioequivalence is established. (Meyer Stmt. at 6).

The insincerity of Ferring's arguments in support of requiring studies on enuretic children should thus be clear. Not only does Ferring fail to offer any data to support such a requirement, but studies conducted on its own behalf directly contradict its current position.

FDA should not require desmopressin acetate ANDA applicants to conduct studies on enuretic children to establish bioequivalence.

III. FDA Should Not Require Studies On Both Approved Strengths Of Desmopressin Acetate Tablets.

Finally, Ferring argues that the two approved strengths of desmopressin acetate, 0.1 mg and 0.2 mg, “do not give proportionally similar drug exposure” and, thus, an ANDA applicant should be required to conduct bioequivalence studies on both strengths. (Ferring Pet. at 1-2, 7-8). In support of its argument, Ferring relies on the AUC and C_{max} of the two strengths. (*Id.* at 7). As an initial matter, if Ferring is correct that plasma concentrations are not an appropriate measure of bioequivalence, Ferring does not explain why AUC and C_{max} should be appropriate to establish non-linearity. (Meyer Stmt. at 6). Ferring cannot have it both ways.

The fact is that the desmopressin NDA studies indicate that the two strengths of desmopressin acetate tablets do give proportionally similar drug exposure, contrary to Ferring’s current contention. (*Id.*). If the C_{max} and AUC in the NDA studies are corrected for strength, the 0.1 mg/0.2 mg ratios are 97% and 85%, respectively. (*See id.* (discussing Chen Review)). Neither 85% nor 97% would be evidence of non-proportionality given the coefficient of variation for AUC of 77-104%. (*Id.*). And the measurement of C_{max}, being less prone to assay sensitivity limitations, may in this case be a more reliable measurement than AUC, particularly given the variability of AUC. (*Id.*). A 0.1 mg/0.2 mg ratio of 97% for C_{max} indicates that the two strengths of desmopressin acetate tablets yield proportionally similar blood concentrations. (*Id.*). Finally, the 0.1 mg and 0.2 mg tablets used in the NDA studies had identical quantities of inactive ingredients. Therefore, they would not be expected to exhibit differences in bioavailability. (*Id.*).

Because Ferring’s own data suggests that the two strengths of desmopressin acetate tablets give proportionally similar drug exposure, and Ferring offers no valid reason to conclude otherwise, FDA should not require ANDA applicants to conduct studies on both approved strengths of desmopressin. (*Id.*). Once again, Ferring has demonstrated that it seeks only to construct unnecessary and expensive barriers to delay or prevent the market entry of less-expensive generic drugs.

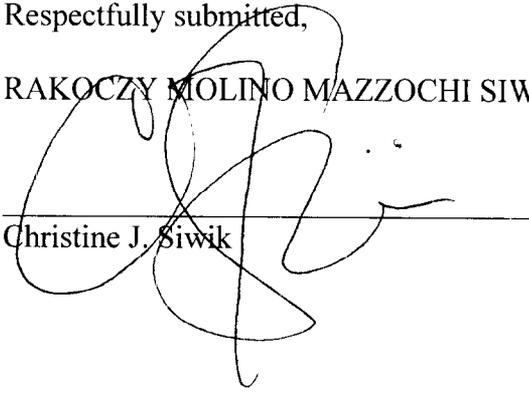
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CONCLUSION

The arguments made in Ferring's petition have no basis in science, fact, FDA regulations, or Guidance. Ferring's citizen petition merely is another prong of its strategy to block generic competition. Using current bioequivalence study procedures and data, generic companies can reliably establish bioequivalence to the RLD using a PK study. FDA should, therefore, deny Ferring's petition in its entirety.

Respectfully submitted,

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